Fracture healing is a complex process in which mechanical forces are essential for the regeneration of bone tissue. Mechanical loading can induce osteogenesis through the process of mechanotransduction. Current data on how mechanical loading stimulates fracture healing in weight-bearing long bones are presented. The role of mechanosensors, loading-induced interstitial fluid flow, streaming potentials, the biophysical environment of the fracture gap and the significance of timing, strains and distribution of mechanical stimulation in long bone fractures are reviewed. Remodelling and biomechanical concepts of fracture healing are discussed from a clinical perspective.

Keywords: fracture healing; long bones; mechano-biology; functional adaptation; mechanotransduction.

INTRODUCTION AND BACKGROUND

The general principle of the adaptation of form and function of bones to mechanical stimuli is defined by Wolff's law (1892): “Every change in the function of a bone is accompanied by certain changes in the internal architecture and external form of the bone according to mathematical laws”. Wolff believed that the mass, internal architecture and outer shape of the growing bone change in order to counter static tensile and pressure loads. Wilhelm Roux (1881) proposed the idea that bone adapts dynamically to mechanical loads by a “quantitative self-regulating mechanism” controlled at the cellular level and dependent on alternating mechanical stimuli (39,107).

It is now clear that, throughout life, bone tissue differentiation is influenced by mechanical loading. Bone has the potential to regenerate fully after damage and to maintain a relatively constant bone mass. The individual bone cells in bone tissue have been identified. The activity of these cells is capable of modelling the structure of the bone in response to changing functional demands via a dynamic balance of growth and resorption resulting in functionally altered bone tissue with changed load resistant properties (17,69,71,97,102).

Fractures occur at all ages of life. Those in weight-bearing long bones are common and detrimental to the function of the locomotor apparatus and they consume time and resources. Through the capacity to induce osteogenesis, mechanical forces play an essential role in the healing of fractures and in remodelling. Fracture healing in general is a process with marked complexity which is also...
influenced by hormonal, vascular, pharmacological and cell biological factors (43,62,78,79,89). If fracture union fails, there may be a delayed union, or non-union with arrested bone healing. The problems associated with improper healing can to some extent be understood in a mechanobiological setting. Thus, an understanding of mechanobiology is an important aspect of understanding fracture healing.

This review article presents biomechanical concepts of fracture healing in weight-bearing long bones, combining knowledge from anatomy, biology, engineering, pathology and clinical research. The reference list is far from exhaustive but the author has tried to confine himself to key works that are specifically relevant in addressing the issue of mechanical stimulation of fracture healing. The following words have been used singly and in combinations in a literature search on MEDLINE: Fracture healing, Wolff’s law, osteoblast, osteoclast, mechanobiology, remodelling, functional adaptation, mechanotransduction, mechanostat, long bone, gap size, cyclical strain, axial stress.

**BONE BIOLOGY**

Histologically, bone tissue exists in a woven and a lamellar form. In fracture healing, woven bone is produced first and is later remodelled to lamellar bone. Lamellar bone is found in a solid form, compact bone, and in a thinner form, cancellous bone. Compact bone is covered with periosteum on the outside and with endosteum on the inside, with concentrically arranged parallel columns of bone lamellae formed by appositional growth from the periosteum and the endosteum. The lamellae surround the Haversian canals which contain blood and lymph vessels and nerve threads. The canals are interconnected and are in contact with the endosteum via Volkmann canals. Cancellous bone consists of a trabecular network with interposed bone marrow. Cancellous bone does not contain Haversian systems. Its osteocytes exchange metabolites with sinusoids in the marrow via canaliculi (fig 1) (30,47,92,101).

There are four types of bone cells: osteoblasts, osteoclasts, osteocytes and bone lining cells. Osteoblasts and osteocytes are differentiated from mesenchymal stem cells and are regulated by growth and sex hormones, leucotrienes, interferons and cytokines. Osteoblasts produce collagen which is a component of the bone matrix, which also contains non-collagenous proteins and growth factors important in fracture healing. Osteoclasts lie in depressions on the bone surface. They are multinucleated cells derived from the macrophage-monocyte line. They produce proteolytic enzymes whereby bone resorption is initiated (35,45,92). Bone lining cells are flat osteoblasts that envelop the bone surface. They are thought to regulate the excretion of calcium and phosphate and to possess receptors for hormones and humoral factors that initiate bone healing and remodelling. The periosteum is composed of a fibrous layer through which the outer layers of the long bone are nourished (6,89).

Osteoblasts are gradually trapped in lacunae in the matrix and transform to osteocytes which probably have a mechanosensory function. Between the Haversian canals and the lacunae are canaliculi through which extracellular fluid flows bringing essential nutrients. The surface of the osteocytes carries a cilium that may be sensitive to fluid shifts in lacunae triggered by physical activity (105). The osteocytes are connected to osteoclasts, osteoblasts and other osteocytes via canaliculi and specialized gap junctions. In this way, a large cellular network or syncytium is formed. This network mediates contact between periosteal and endosteal cells and can facilitate the activation of a very large number

---

Fig. 1. — The microscopic structure of long bone tissue
of cells when responding to a particular stimulus such as loading (11,24,61,65,94).

When a fracture occurs, the blood vessels of the periosteum rupture, resulting in haematoma and bone necrosis, and the tissue is invaded by polymorphonuclear leucocytes, macrophages and mononuclear cells. The haematoma is organized by ingrowth of vessels, and fibroblasts produce fibrous tissue. In this reparative phase, chondrocytes are active and woven bone is laid down by endochondral ossification with the formation of a provisional fibrocartilaginous callus. Osteoblasts are gradually differentiated and a bridging mineralized callus is formed internally and externally over the fracture. This is called bony union (14,63). Over the ensuing weeks, osseous ingrowth of the callus closes the fracture and the remodelling phase begins. Remodelling goes on for years with increasing deposition of organized mature lamellar bone. If the fracture is repositioned, the normal microscopic architecture of the bone can be recreated (46).

REMODELLING

Remodelling of a fracture is a long-term cellular adaptation response to mechanical loading. It represents a homeostasis between osteoblast and osteoclast activity and thereby between synthesis and resorption of bone (fig 2). During bone remodelling, osteoclasts and osteoblasts are activated as a Basic Multicellular Unit (BMU) in a coordinated coupled sequence. First, the osteoclasts resorb old or damaged bone. This is followed by osteoblastic deposition of bone lamellae around Haversian canals and on trabecular surface (10,21,68,80,78). BMUs also repair microfractures. This type of repair strengthens the bone without altering its mass or outer form. The regenerative capacity of the bone can be exceeded before the bone tissue can remodel. This can lead to a macrofracture (62,72,96).

Children and adolescents have an extraordinary ability to heal and remodel. A callus develops quickly and a gradual reduction of any angulation occurs. Long bones having healed at angles up to 25-30 degrees, can potentially remodel to their anatomical shape (9). Not only is this caused by active bone healing and remodelling at the fracture site, but also because the physes are active. Thereby, fracture angulation can partly be corrected by the growth of the bone. The ability of the adult bone to remodel angulation in the diaphysis is limited and slower (23,66,73,79).

**Fig. 2.** — Bone remodelling is an expression of a homeostasis between bone synthesis and loss of bone mass
THE MECHANOSTAT THEORY (MST)

A theoretical way of understanding the remodelling process is Frost’s MST (31). The MST proposes that weight-bearing bones are equipped with genetically determined physiological signal thresholds for maximal and minimal strains. It is assumed that bone strains regulate the bone mass by a feedback system analogous to the way regulation of temperature in a room can be controlled by a thermostat. When the upper strain threshold is reached, the bone is remodelled by BMUs resulting in net bone synthesis. If the load drops below a lower strain threshold, bone resorption is predominant. The net bone mass diminishes, accentuating the porosity of the bone with reduced stiffness and strength. Loads between these two thresholds will induce remodelling with no net change of the total bone mass (fig 3)(32,95).

While fractures are often caused by trauma or specific bone pathology, macrofractures are also caused by accumulation of microfractures in healthy bone (stress fracture) after continuous loading (15). This type of fracture, MDx, is caused by loading strains over a pathological threshold. It can contribute to aseptic bone loosening of implants because of reduced osseointegration between bone and implant (31). The feedback system is normally able to register and repair MDx by activating BMUs, enabling weight-bearing long bones to strengthen their resistance to muscular traction or fatigue phenomena. This functional adaptation is controlled by smaller strains between the upper and lower physiological thresholds throughout life (32). It is plausible that such thresholds could shift due to non-mechanical factors such as hormonal, humoral or metabolic ones. For example, calcium or oestrogen depletion as seen in osteoporosis or long-lasting mechanical inactivity as in immobilization, might shift the thresholds to the right on the graph in figure 3. In this way, greater loads would be required before the bone tissue was stimulated to bone synthesis. On the other hand, multiple microfractures could lower the thresholds, so less stimulation would be required before bone synthesis was induced. The thresholds might also shift with aging so that bones of younger individuals require less stimulation for bone formation than those of older individuals (1,7,36).

MECHANOTRANSDUCTION

Long bones are loaded and deformed by combinations of bending, shearing, twisting and axial compression (58). Bone adapts in such a way that the density, mass, synthesis and organization of the trabeculae in the bone tissue are most dense and active in directions corresponding to the loading axes where external compression and tensile loads are the greatest (13,57). Increased functional loading results in bone hypertrophy and a large number of trabeculae per unit volume as well as greater bone

---

Fig. 3. — The Mechanostat Theory
density (BMD). The thicker bones of a trained individual become more resilient to loading. Atrophy and osteopenia are caused by patients being bedridden, by cast immobilisation or by muscle paralysis (26,33,98,104). Functional adaptation is dependent on cellular processes in which bone cells must be able to detect applied mechanical forces. This happens via mechanotransduction – the process by which mechanical energy is converted to electrical or biochemical signals in bone cells (100).

During axial loading of long bones in vivo, the greatest force of compression is measured on the concave side, with the greatest tension being on the convex side (23,29). Fluid probably flows in the canaliculi from areas of compressed high pressure matrix areas to those of lower pressure. This results in rising hydrostatic pressure gradients within the matrix, displacement of interstitial fluid, deformation of lacunae and activation of mechanosensory osteocytes. The mechanosensory osteocytes probably transmit load-provoked signals via canaliculi and gap junctions both in the fracture scenario and in intact bone (2,44,65,99).

When a fracture is compressed and deformed beyond a certain threshold, the hydrodynamic load generates an electrophysiological response in the form of electric streaming potentials, the phenomenon of piezoelectricity (94). A negative potential is produced on the compressed concave side of the surface of the fractured bone. Here, osteoblasts are relatively more active compared to the convex side. A positive potential is registered on the convex side with mainly osteoclast activity and resorption (23). It is possible that streaming potentials activate mechanotransduction and induce osteogenesis (59,64) for example by opening voltage-controlled channels in osteoblast cell membranes. If mechanical loading elicits a signal induced by fluid flow, this signal might be too weak to activate the mechanosensors per se. Streaming potentials might enhance the amplitude of the fluid flow induced signal on the cell surface and stimulate mechanotransduction by activating the mechanosensors in a synergistic way. Neighbouring groups of osteocytes, osteoblasts and bone lining cells could be activated by the electric fields generated (72). Their bone forming activity would generate further streaming potentials leading to a self-enhancing mechanotransductive reaction (61,66).

The external mechanical signal must be coupled to an intracellular biochemical activity. On the molecular level, it is possible that mechanical stimulation elicits a molecular signal that initiates synthesis of proteins on the organ or cellular level. In vitro, osteocytes and bone lining cells exposed to fluid flow or mechanical strain produce second messengers and paracrine factors. Cytokines, prostaglandins and nitric oxide might be able to make stem cells differentiate into osteoblasts (7,76).

There seems to be a delay of 3-5 days before bone synthesis is seen on the surface. This delay could reflect the time it takes to transmit the mechanical signal to osteoprogenitor cells in the bone marrow and initiate differentiation into active osteoblasts (19).

**THE BIOPHYSICAL FRACTURE ENVIRONMENT**

Local tissue stress and strain not only alter the pressure on the bone cell, but also influence cell differentiation. In the fracture gap after fixation, hydrostatic cyclical pressure is initially relatively low and interfragmentary strains are relatively high. According to Prendergast et al (82), it is here that fibroblasts are differentiated. In the next phase, callus and collagen are produced by fibroblasts and the matrix stiffens. As the callus grows stiffness increases in the fracture.

The matrix permeability decreases with rising hydrostatic matrix pressure while fracture shear strains decline. In this environment, increasing numbers of chondrocytes differentiate and endochondral ossification begins (25). Gradually, as more collagen matrix is produced, the strain...
declines further, more osteoblasts accumulate and ossification predominates. As the biophysical environment gradually changes, the number of chondrocytes diminishes and the number of osteoblasts increases. It is plausible that mesenchymal cells cannot differentiate into bone cells or chondrocytes unless a suitable biophysical fracture environment for tissue differentiation is present (20,58). Thus, for osseous healing to occur, the fracture environment has to be exposed to strain rates that elicit a bridging callus with increased collagen synthesis and rising hydrostatic pressures.

**BIOMECHANICAL STUDIES OF FRACTURE HEALING**

Animal and clinical studies have investigated the healing of osteotomies and fractures in long bones using more or less rigid fixation with or without artificial mechanical stimulation and applying different weight-bearing programmes. Animal experimental studies are biased as they are based on osteotomies instead of real fractures (77). Clinical studies often include severe fractures that cannot be treated with cast immobilisation and are therefore treated with an external fixator.

Both fracture and osteotomy studies indicate that tissue strains within certain time intervals are important for healing (16,28,29,38,67,91). There seems to be a weak osteogenic response to ongoing (static) strain compared to cyclical (dynamic) strains (2, 5,37,50,52,70,86,87). Osteogenesis seems to be more active in areas of relatively limited strain while there is a tendency to formation of fibrous tissue in areas with higher strains (fig 4) (3,21). Clinical studies show that fracture instability (with consequently high strains) can lead to delayed healing and non-union. Therefore, fractures are osteosynthesized as stably as possible (49,53,74). It is difficult to state which role load magnitude plays, but fairly large loads can precipitate very large strains that can be inhibitory to osteogenesis and can promote pseudoarthroses or implant failure (42,51,83). The importance of speed and frequency of loading in osteogenesis is unclear but a few studies indicate that several daily load cycles can be more osteogenic than one single loading sequence (12,28, 84).

In delayed healing, it can be beneficial to "dynamize" the fracture by compression (or traction) to promote healing (4,25). Axial compression over the fracture site lowers interfragmentary

---

**Fig. 4.** — Strain and hydrostatic pressure are determinants of ossification at the fracture site.
movement (55,90). The strain in the fracture site diminishes and a mineralized rather than a fibrous callus is formed. Reduced interfragmentary movement results in greater bending resistance in the callus and in denser lamellation in the bony bridge (20). On the other hand, fixation in the initial phase of the healing process can be so rigid that osteogenic strains are not elicited due to very limited movement of fracture fragments. The stimulation of callus formation is weakened and a non-union might occur (27,56).

Relatively large fracture gaps of more than 2 mm inhibit fracture healing. Therefore, simple diaphyseal fractures should be fixed with the smallest possible gap (20,51). These observations are possibly explained by the large interfragmentary strains found in a relatively large gap, which do not stimulate ossification (34). It can also take more time to attain osseous healing in a large gap because enough callus has to be formed to reduce the movements and attain stability over the fracture. A large amount of callus is not necessarily mechanically stable because interfragmentary movements over more than 1 mm result in more connective tissue in the fracture (20). Angiogenesis in the callus may also possibly be destroyed by too much motion in a larger gap (103).

The timing of the mechanical load is important. Axial fracture loading seems to be beneficial early in the course of fracture treatment. Early artificial mechanical stimulation with pumps or springs can be beneficial because active loading is limited in the early phase due to pain, restriction in weight-bearing or because this period is particularly sensitive to mechanical stimuli (38,52).

In a series of mechanically loaded rat tibiae, Robling et al (85) found that bone cells regained their mechanosensitivity with a rest period of 8 hours between loading bouts. Enhanced bone formation was found compared to groups with shorter rest periods. The sensitivity of the bone cells to a mechanical stimulus seemed to be saturated fairly quickly. This was followed by a period in which the cells regained their mechanosensitivity and were able to respond to mechanical stimulation again. It was proposed that shorter periods of activity with relatively high loading rates with interposed resting periods of 4-8 hours elicit a more effective osteogenic stimulus in fractures compared to single daily loading sessions.

Electrical and electromagnetic fields in bone tissue stimulate bone formation in some in vitro and in vivo studies. A physiological osteoinductive electrical effect is simulated by implanting negatively charged electrodes with small currents in fractures. In in vivo studies, osteotomies and fractures were exposed to electrical stimulation. Thus, a mechanical stimulus was present at the same time as the electrical one. It is possible that the electrical stimulus in itself does not induce osteogenesis but solely enhances mechanical stimuli. In the clinical setting, atrophic pseudoarthroses do usually not heal with electromagnetic stimulation while hypertrophic pseudoarthroses, where a mechanical stimulus potential is present, can heal. In an electrically stimulated fracture environment, mechanical or biochemical stimuli must plausibly be present as suitable osteoinductive co-stimuli (47,81,94).

Ultrasound possibly enhances the healing processes in the inflammatory, the reparative and the remodelling phases. Low intensity ultrasound has been used as an adjuvant in conservatively treated fractures but does not seem to influence any singular process or mechanism during mechanotransduction (40,41,88).

When bone tissue is loaded in relatively fast, forceful or frequent sequences, the hydrostatic pressure and cell strains increase intermittently. Jacobs et al (48) demonstrated that the activity of human foetal osteoblasts is directly proportional to the magnitude of fluid flow they are exposed to. They propose that fluid flow during loading is important for the osteogenic response. Fluid flow through canaliculi and in the lacunae of the osteocytes seems to be elicited by cyclical loading. This supports the results from animal experiments and clinical studies which show that osseous functional adaptation in weight-bearing long bones in vivo takes place only by dynamic load induction (68).

All in all, there are biomechanical limitations to when a mineralized callus can be formed. The biomechanical parameters that are significant for the fracture healing environment in physiological scenarios are therefore combinations of loading
cycle frequency, the magnitude, duration and timing of each loading sequence, fracture gap size and the velocity whereby bone tissue deforms with altered cellular strains. In summary, the dynamics and distribution of mechanical loading in fractures are important. Blood perfusion, supplies of metabolites, hormones, growth factors and cytokines are other essential factors for fracture healing (table I), but their roles are not addressed in this review (12,34,49,54,93).

**BONE HEALING IN THE CLINICAL SETTING**

Developing optimal bone bioengineering for clinical use is challenging due to the relative paucity of accurate experimental data on the bone healing process. Data from animal studies and studies on cell cultures predominate while there are relatively few clinical studies on mechanotransduction. However, it is clear that a certain fracture environment must be present or created to allow for fracture healing.

The ideal level of strain for each stage of fracture healing for individual fractures is not known. The fracture healing process is seen to be acutely sensitive to small periods of daily axial strain applied in the initial healing phase. However, the fracture gap and the amplitude of movement should be kept to under 2 mm, and to between 0.2 and 1 mm, respectively (16,34,106). Higher strain amplitudes may be tolerated for certain fracture types such as spiral or comminuted fractures (56). If indirect fracture healing is the goal, micromotion of the fragments along the axes is beneficial for the formation of soft callus while joint congruency and axial and rotational positions have to be maintained. Controlled fracture site movement with some external fixators, certain osteosynthesis implants and active loading can dynamize the bone tissue by compressing the bone fragments (49). Such dynamic mechanical loads can move the biophysical fracture environment towards osteogenesis according to the principles of mechanotransduction.

In the nonambulant phase immediately after injury or surgery, when patients often cannot bear weight through the injured limb due to either pain or to restrictions in loading, there is minimal loading and movement of fractured long bones. This may be the time when externally imposed stimulation, produced by for example a micromovement module using a pneumatic pump, could provide axial strain to the healing fracture. Active loading by the patient may then supervene as healing progresses by adjusting the axial rigidity of a fixator frame or beginning to bear weight to allow for optimum axial strain.

In the final period of healing, the formation of calcified callus is compromised by vigorous mechanical stimulation unless stably fixated (56) and motion should be limited, which is naturally achieved by the increasing stiffness of the ossifying callus. Thus, mechanical stimulation early on may be most effective.

---

Table I. — Inhibitors and stimulators of bone healing (4,11,30,44,110)

<table>
<thead>
<tr>
<th>Biochemical factors</th>
<th>Medical and pharmacological factors</th>
<th>Biological products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D</td>
<td>Smoking</td>
<td>Autologous and allogenous bone grafts</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>Malnutrition, alcohol consumption</td>
<td>Bone Morphogenetic Proteins</td>
</tr>
<tr>
<td>Interleukines</td>
<td>Diabetes mellitus, vascular disease</td>
<td>Fibroblast Growth Factors</td>
</tr>
<tr>
<td>Leukotrienes</td>
<td>Rheumatoid arthritis and other autoimmune diseases</td>
<td>Insulin-like Growth Factors</td>
</tr>
<tr>
<td>Sex hormones</td>
<td>Hypogonadism, hypothyroidism, hypoparathyroidism</td>
<td>Platelet-derived Growth Factor</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Age, neurovascular damage, low habitual locomotor function</td>
<td>Tissue engineering ?</td>
</tr>
<tr>
<td>Tumor necrosis factor</td>
<td>Pharmacotherapy : NSAIDs, steroids, bisphophonates, immune modulating drugs</td>
<td>Gene therapy ?</td>
</tr>
</tbody>
</table>

---

Acta Orthopaedica Belgica, Vol. 74 - 3 - 2008
Nearly all fracture treatment regimens necessitate the use of an artificial support to stabilize the bone fragments. Therefore, it is the fixation device that will play a major role in determining the mechanical environment at the fracture site and, thus, the subsequent pattern of healing. Bearing MST in mind, a fracture implant should logically be anchored in such a way that optimal osseointegration and stability are achieved and that a loading stimulus over the threshold for bone synthesis is present.

In the healing phase, the implant should be stable and keep the bone tissue over the threshold for net synthesis of bone matrix but under the threshold for microdamage. Loading under the lower threshold for bone loss, on the other hand, can contribute to aseptic loosening of the implant. In order to optimize bone healing, is it desirable that implants should be constructed to distribute loads evenly over the entire fracture site (31, 32). Anchoring materials must be resilient to loading over a long period of time. The anchoring must be constructed in such a way that a limited amount of bone is lost in case of implant failure. It should be biocompatible so that it does not elicit inflammation with subsequent osteoclastic bone resorption precipitating loosening or delayed healing (8, 18, 22, 60, 75).

CONCLUSIONS

Bone healing is a continuous dynamic process in which ongoing bone synthesis and bone resorption are decisive for the bone tissue’s architecture and strength. The terms mechanotransduction or osseous functional adaptation present themselves as precise terms for biomechanically regulated fracture healing. Today, there is an understanding of the cellular mechanisms and interactions in fracture healing and adaptation in weight-bearing long bones. Functionally integrated bone units have not been identified such as for instance the physiologic mechanism of the renal nephron or the liver sinusoid units.

Optimal mechanical conditions for fracture healing in the different phases of healing are not known. With further focused experimental and clinical research such as the ostectomy series of Claes et al. and Kenwright’s large clinical fracture series, perhaps also with axially stable internal fixation, it might be possible to clarify how and when mechanical stimuli cause fracture healing in the three healing phases. Such results on optimal load-induced bone repair in advanced fracture treatment could be utilized directly in the development of osteoinductive implants, adjuvant molecular biological therapies and efficient postoperative loading regimes. This in turn may lead to a better understanding of the basic concepts presented here.

REFERENCES

Acta Orthopædica Belgica, Vol. 74 - 3 - 2008

45. Huiskes R. If bone is the answer, then what is the question ? J Anat 2000 ; 197 (pt 2) : 145-56.


